METHOD OF INCREASING TEAR PRODUCTION BY TOPICAL ADMINISTRATION OF CYCLOSPORIN

FIELD OF THE INVENTION

The present invention relates to a method of increasing tear production in a patient suffering from deficient tears in the eye due to an autoimmune dysfunction of the lacrimal (tear) glands. More specifically, this invention relates to a method of treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom, which method includes administering a cyclosporin topically to the patient's eye.

BACKGROUND OF THE INVENTION

The exposed part of a normal eye is covered by a thin tear film. The presence of a continuous tear film is important for the well-being of the corneal and conjunctival epithelium and provides the cornea with an optically high quality surface. In addition, the aqueous part of the tear film acts as a lubricant to the eyelids during blinking of the lids. Furthermore, certain enzymes contained in the tear fluid, for example immunoglobulin A, lysozyme and beta lysin, are known to have bacteriostatic properties.

A sound lacrimal system functions to form and maintain a properly structured, continuous tear film. The lacrimal apparatus consists of the secretory system (the source), the distribution system and the excretory system (the sink). In the secretory system, aqueous tears are supplied by the main and accessory lacrimal glands.

The bulk of the tear film is made of such aqueous tears. The continuous production and drainage of aqueous tear is important in maintaining the corneal and conjunctival epithelium in a moist state, in providing nutrients for epithelial respiration, in supplying bacteriostatic agents and in cleaning the ocular surface by the flushing action of tear movement.

Abnormalities of the tear film include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca or KCS).

In relatively mild cases, the main symptom of KCS is a foreign body sensation or a mild "scratchiness". This can progress to become a constant, intense burning or irritative sensation which can be debilitating to the patient.

More severe forms progress to the development of filamentary keratitis, a painful condition characterized by the appearance of numerous strands or filaments attached to the corneal surface. Recent evidence suggests that these filaments represent breaks in the continuity of the normal corneal epithelial cells. The shear created by lid motion pulls these filaments, causing pain. Management of this stage of KCS is very difficult.

A frequent complication of KCS is secondary infection. Several breakdowns in the eye's normal defense mechanism seem to occur, presumably attributable to a decrease in the concentration of antibacterial lysozyme in the aqueous tears of a patient suffering from KCS.

Although KCS can develop in the absence of any other overt systemic abnormality, there is a frequent association of KCS with systemic disease. KCS can occur as part of a larger systemic involvement known as Sjogren's syndrome. This classically consists of the triad of dry eyes, dry mouth, and arthritis.

Histologically in KCS (as part of Sjogren's syndrome or in isolation), the initial changes seen in the lacrimal gland are those of focal lymphocytic and plasma cell infiltrates associated with degeneration of glandular tissue. These changes resemble those seen in autoimmune disease in other tissue, giving rise to the speculation that KCS has an autoimmune basis.

Sjogren's syndrome is recognized as an exocrine gland dysfunction. Characteristically, the lacrimal glands show a mononuclear-cell infiltration that ultimately leads to destruction of the glandular structure.

Conventional treatment of KCS is symptomatic.

Normally, aqueous-deficient dry eye states are treated by supplementation of the tears with artificial tear substitutes. However, relief is limited by the retention time of the administered artificial tear solution in the eye. Typically, the effect of an artificial tear solution administered to the eye dissipates within about thirty to forty-five minutes. The effect of such products, while soothing initially, does not last long enough. The patient is inconvenienced by the necessity of repeated administration of the artificial tear solution in the eye as needed to supplement the normal tears. Moreover, such treatment merely acts to alleviate the symptoms of the dry eye state and does not cure any underlying disorders or causes of the dry eye state.

Histologic studies of the lacrimal glands in patients suffering from Sjogren's syndrome have shown some evidence of lacrimal gland inflammation. Such inflammation may simply be due to the normal aging of the patient. It has been suggested that the use of antiinflammatory agents might serve to decrease the glandular inflammation. The systemic use of corticosteroids has been advocated in these conditions. However, the merit of systemic corticosteroids in dry eye states has not been established. In most dry eye cases the hazards of long term use of antiinflammatory agents would seem to outweigh their potential merit.

Surgical procedures have also been suggested in the management of dry eye states. Where there has been significant conjunctival destruction, mucuous membrane transplants have been advocated. It has also been suggested that parotid (saliva) duct transplantation can be useful in the management of dry eyes. However, since surgical alterations to combat dry eye conditions constitute such a drastic remedy and the benefit resulting from these alterations is questionable, these methods are usually used in dry eye patients only as a last resort.

It has also been suggested to administer orally a dilute solution of pilocarpine to stimulate the autonomic nervous system to effect increased aqueous tear production. This method of treatment has not met with universal favor because of the unpleasant side effects of ingested pilocarpine.

Animal models of Sjogren's syndrome have been instrumental in basic ophthalmic research. A Sjogren's-like disease has been found in dogs with systemic lupus erythematosus.

Canine KCS is a common, chronic progressive, and potentially blinding disease. A continuum of corneal and conjunctival lesions ensues from the dry eye state. The cause of KCS in canines is often not identified. Usually, canine KCS is not an isolated ophthalmic disease. It has been speculated in Kaswan et al., Am. J. Vet. Res. 46, 376-383 (1985), that most cases of canine KCS occur via autoimmune mechanisms.

The term autoimmunity is used to indicate immunologic self injury, but not a singular etiology. Autoim-